Functional Connectivity with Low Frequency BOLD Fluctuations

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- Functional connectivity can be defined as a descriptive measure of spatiotemporal correlations that exist between spatially distinct regions of the brain.(1, 2)
- It has been widely observed that spontaneous low-frequency fluctuations in BOLD-weighted MRI data are correlated between brain regions known to be involved in similar task performance
  - Motor system: (3-5)
  - Visual system: (4)
  - Auditory system: (6)
  - Cognitive systems: (7, 8)

- How To Measure Connectivity with low frequency BOLD fluctuations (LFBF) Example:
  - Data Acquisition:
    - Need high temporal sampling rate to avoid aliasing cardiac and respiratory-rate effects
    - Typical Experiment
    - Subject at rest in 1.5T MRI scanner
    - acquire 2200 images of a single slice through bilateral motor cortex
    - 64x64 image matrix
    - TE/TR/flip=50ms/133ms/30
    - bandwidth=125kHz
    - FOV=24cm, slice thickness=5mm
  - Data Analysis:
    - Lowpass temporal filter (<0.1Hz) timeseries at each pixel(9)
    - Select seed voxel in *a priori* selected region of interest (e.g. primary motor cortex)
    - Calculate cross-correlation of timecourse from seed voxel with every other voxel in acquired volume.
    - Note: for most acquisition strategies, it is NOT necessary to correct for slice-timing offsets due to the low-frequency nature of the effect. If in doubt, correct for slice-time offsets.

- Volumetric acquisition
  - Aliased physiologic noise results in inefficient filter
  - Reduction in specificity of effect(4)
  - Removal of aliased physiologic signals.

- Volumetric Studies-example: 15 slice coronal study (TR=2sec)
  - 512 volumes acquired (17 minutes)
- Network Analysis Techniques:
  - Data Driven Methods
    - Principle Components Analysis

        - Independent Components Analysis
        - Cluster Analysis
    - Hypothesis Driven Method
        - Structural Equation Modeling
- Principle Components Analysis
    - Eigenanalysis of observed spatiotemporal correlations to produce orthogonal components in the direction of maximal variance
    - Advantage: easily performed
    - Disadvantages:
        - Not well-suited for low SNR data (effect of interest should be a major effect on total variance in system)
        - Orthogonality requirement is too stringent for fMRI or connectivity applications
        - Requires post-hoc interpretation
- Independent Components Analysis
    - Assumes time-series data are related by a linear transformation to spatially independent components
    - Separates spatially independent sources contributing to the "entropy" of the system(10)
    - Computationally intensive
    - PCA typically used to reduce degrees of freedom
    - Requires post-hoc interpretation of components
- ICA vs. PCA
    - Example: six independent source images
- Structural Equation Modeling
    - Method to test an *a priori* defined model of path-wise dependence of observable correlations or covariances
    - Application to fMRI or connectivity studies
    - Can test models of functional and/or neuronal connectivity
    - Example:
    - Data Acquisition
        - Grad. Echo EPI, 64x64 matrix, 24cm x 24cm FOV, 2 5mm thick slices, TE/TR/flip=50ms/316ms/30^{o}, 1200 repetitions
        - 3 scans: rest, continuous bimanual tapping, fMRI paradigm with interleaved rest and tapping
    - Data Analysis
        - Anatomic T1's used to define ROI's in (left hemisphere only) precentral gyrus, SMA, putamen, globus pallidus, thalamus.
        - Timeseries from each ROI filtered to remove fluctuations > 0.1Hz.
        - Correlation matrix formed for each CP scan (i.e. resting state, and CP tapping)
        - Path model tested using LISREL8 (Scientific Software International)

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